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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,019	09/21/2001	Chikara Aizawa	SHIM1120	9316

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,019	AIZAWA ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/14/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7 and 16-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7 and 16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 7, 16, 17-23 are pending.

Response to Amendment

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. The new examiner is setting forth a Non-Final Action below.

Claim Objections

2. Claim 22 is objected to because of the following informalities: Claim 22 recites the term "is" on line 2, but lists a plurality of toxins; the phrase "selected from the group consisting of " appears to be missing. Appropriate correction is required.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 1-2, 7, 16, 22 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Domenighini et al (WO93/13202) in light of extrinsic evidence provided by Rappuoli et al (US 20040028690 A1 February 12, 2004 or Rappuoli 20050106180).

5. Domenighini et al disclose the instantly claimed invention directed to a purified and attenuated mutant heat-labile toxin of pathogenic E.coli and mutant cholera toxin, wherein the mutant E.coli heat-labile toxin and mutant cholera toxin are mutated at positions **Arg-7** (see page 49, claim 2), **Ser63-Lys** (page 49, claims 1 and 3) , **Ser-61** ((page 49, claims 1 and 3), **Glu-112** (see page 49, claim 2), the toxins being purified to at least 98% (see page 21, lines 8-9). The mutant detoxified/attenuated toxins have "a toxicity of less than 0.01% of the naturally occurring toxin counterpart (see page 8, lines 5-6) " and inherently would evidence adjuvant activity in light of extrinsic evidence provided by Rappuoli et al that teach the toxins to have adjuvanting activity(see titles of Rappuoli et al, cholera toxin and E.coli heat-labile toxins are ADP-ribosylating toxins).

While the toxins of Domenighini et al were obtained by a different process, the attenuated toxins of Domenighini et al are the same or equivalent toxins now claimed because Domenighini et al disclose the same or equivalent positions for mutation as described in Applicant's Specification in Table 1, on page 12 and Table 3, page 40 LTR7 and in light of extrinsic evidence provided by Rappuoli et al (US 20040028690 A1 February 12, 2004 or Rappuoli 20050106180) that the mutant cholera and heat labile enterotoxins evidence adjuvanting activity. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent

characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

The purification or production of a product by a particular process (i.e. the instant recombinant) does not impart novelty or unobviousness to a product when the product is taught by the prior art. This is particularly true, when the properties of the product are not changed by the process in an unexpected manner. *In re Thorpe*, 227 USPQ 964 (CAFC 1985); *In re Marosi*, 218 USPQ 289, 292-293 (CAFC 1983); and *In re Brown*, 173 USPQ 685 (CCPA 1972). Therefore, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product *per se*, even when limited to the particular process, is unpatentable over the same product taught by the prior art. *In re King*, 107 F.2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); *In re Merz*, 97 F.2d 559, 601, 38 USPQ 143-45 (CCPA 1938); and *United States v. Ciba-Geigy Corp.*, 508 F.supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

6. Claims 1-2, 16, 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al (1994).

7. Tang et al disclose a purified attenuated Vibrio parahaemolyticus thermostable hemolytic toxin, wherein the toxin is a mutant toxin that has been purified to homogeneity (see page 3299, col. 2, paragraph 4; page 3300, col. 2, paragraph 7 "purified to homogeneity"; Fig. 1, page 3301). While Tang et al does not discuss the claimed functional limitation of "adjuvant", the product of Tang et al is the same or equivalent purified and attenuated toxin and therefore anticipates the instantly claimed invention as now claimed.

Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art

composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

The purification or production of a product by a particular process (i.e. the instant recombinant) does not impart novelty or unobviousness to a product when the product is taught by the prior art. This is particularly true, when the properties of the product are not changed by the process in an unexpected manner. *In re Thorpe*, 227 USPQ 964 (CAFC 1985); *In re Marosi*, 218 USPQ 289, 292-293 (CAFC 1983); and *In re Brown*, 173 USPQ 685 (CCPA 1972). Therefore, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product *per se*, even when limited to the particular process, is unpatentable over the same product taught by the prior art. *In re King*, 107 F.2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); *In re Merz*, 97 F.2d 559, 601, 38 USPQ 143-45 (CCPA 1938); and *United States v. Ciba-Geigy Corp.*, 508 F.supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

8. Claims 1, 3 are rejected under 35 U.S.C. 102(e) as being anticipated by Ulrich et al (US Pat. 6,399,332, effective filing date June 25, 1997).

Ulrich disclose purified and attenuated mutant SEA and SEB mutants (see col. 16, line 43 "*All protein preparations were >99% pure*"). Ulrich et al teach the genetically attenuated super antigen toxins (abstract) to be produced by mutations to specific amino acids within the staphylococcal toxins A and B (see quoted narrative below).

"Detailed Description Text (102):

The **SEA** vaccine L48R, Y89A, D70R (A489270) and **SEB** vaccine Y89A, Y94A, L45R (B899445) were used to immunize rhesus monkeys. The animals received a total of three i.m. injections (10-20 .mu.g/animal), given at monthly intervals. Rhesus monkeys that were injected with these vaccines had no detectable increase of serum cytokines and no apparent toxicity. The serological response of animals vaccinated with three doses of **formalin**-treated **SEB toxoid** (100 .mu.g/injection) gave results comparable to one or

two injections with B899445 (Table 7), suggesting that the recombinant vaccines were very immunogenic. Immunized rhesus monkeys survived a lethal challenge with >10 LD50 of wild-type **SEB** (Table 7, 8). Collectively, these results suggest that the engineered **SEB** vaccine is safe, highly antigenic and effective at protecting the immunized individual from lethal aerosol exposure to **SEB**."

Ulrich et al also discloses formalin treated natural SEB toxoid, the SEB (staphylococcus Beta toxin) is a protein treated with formalin to attenuate the toxin (abstract). The natural SEB toxin is a protein that was purified and then treated with formalin to attenuate its' toxicity.

TABLE 6

Mice immunized with attenuated forms of staphylococcal enterotoxin A (SEA) produce high titers of neutralizing antibody

Immunizing agent	Dose (µg/mouse)	Anti-SEA antibody titer[a]	No. live/total
WT	2	10,000–50,000	10/10
	10	10,000–50,000	10/10
K14E	2	5,000–10,000	8/10
	10	10,000–50,000	10/10
Y64A	2	5,000–10,000	6/10
	10	10,000–50,000	10/10
Y92A	2	1,000–5,000	2/10
	10	10,000–50,000	10/10
Adjuvant		50–100	0/10

NOTE. Mice were given 10 LD_{50} of wild type (WT) SEA challenge followed by potentiating dose of lipopolysaccharide (150 µg/mouse) 3 h later.
[a]Reciprocal of serum dilution resulting in optical density reading four times above negative controls (wells containing either no SEA or no primary antibody).

TABLE 7

Rhesus monkey antibody responses to vaccine B899445. One injection of B899445 outperforms three injections of SEB toxoid

Vaccine[1]/animal #	Antibody response[2]	% Inhibition of T-cell response[3]	Survival SEB >20 × LD50 challenge[4]
preimmune sera/pooled	0.161	5	dead
toxoid/1	0.839	0	dead
toxoid/2	0.893	34	live
toxoid/3	1.308	57	live
toxoid/4	1.447	55	live
B899445/1	1.788	69	live
B899445/2	0.78	49	live

[1]Rhesus monkeys were immunized with one dose (20 µg injection) of B899445 vaccine or three doses of formalin-treated SEB toxoid (100 µg/injection) one month apart; both used Alum adjuvants.

Ulrich et al does not discuss the functional limitation of "adjuvant", but produces the same or equivalent product as not claimed and therefore inherently anticipates the instantly claimed invention as now claimed.

9. Claims 1-3, 7, 16, 17-23 are rejected under 35 U.S.C. 102 (b) as being anticipated by Fujita ET al (US Pat. 5,101,019, March 1992).

Fujita et al disclose a purified and attenuated pertussis toxin, wherein

the natural toxin was purified toxin by eliminating 99.9% of endotoxin (see col. 1, line 53; col. 3, lines 32) which is further purified by zonal centrifugation which includes sucrose-gradient centrifugation (see col. 3, lines 39-46 also see col. 6, Example 1, lines 11-39), once purified the pertussis toxin is

attenuated/ detoxified with formalin (see col. 3, lines 49, and 55;). The formalin incubation temperature was 39^0C (see col. 6, lines 50-51).

While Fujita et al does not discuss the adjuvanting activity of the mutant Pertussis toxin, Pizza et al carried out the same or equivalent methods steps and produced the same or equivalent mutant/attenuated Pertussis toxin as now claimed. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

The purification or production of a product by a particular process (i.e. the instant recombinant) does not impart novelty or unobviousness to a product when the product is taught by the prior art. This is particularly true, when the properties of the product are not changed by the process in an unexpected manner. *In re Thorpe*, 227 USPQ 964 (CAFC 1985); *In re Marosi*, 218 USPQ 289, 292-293 (CAFC 1983); and *In re Brown*, 173 USPQ 685 (CCPA 1972). Therefore, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product *per se*, even when limited

to the particular process, is unpatentable over the same product taught by the prior art. *In re King*, 107 F.2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); *In re Merz*, 97 F.2d 559, 601, 38 USPQ 143-45 (CCPA 1938); and *United States v. Ciba-Geigy Corp.*, 508 F.supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

10. Claims 1-2, 7, 16, 17-18, 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Pizza et al EP 0396964 in light of extrinsic evidence provided by Rappuoli (US PG-Pub 2002/0187154) who teaches detoxified Pertussis toxin evidences adjuvant activity (title, abstract claims.)

Pizza et al EP 0396964 disclose the instantly claimed invention directed to: and isolated and purified Pertussis toxin that is a mutant attenuated form of the natural pertussis toxin, the toxin being 99% pure (see page 14, line 41) and mutated at position 129 (see Table II for various mutants of Pertussis toxin, especially position 129), and treated with formalin (formaldehyde is another name for formalin, see page 21, Example 6).

Pizza et al also disclose a method for obtaining a purified and attenuated toxin composing the steps of :

Purifying the mutant toxin, wherein the toxin is pertussis toxin purified to 99% purity (see page 14, line 41) and

Attenuating/stabilizing the mutant toxin obtained in step (a) by incubating the toxin in the presence of formalin at a temperature of between 5° to 40°C, wherein the temperature was 37°C (see page 21, lines 10-16 ; page 7, lines 9-10 and 52-54).

While Pizza et al does not discuss the adjuvanting activity of the mutant Pertussis toxin, Pizza et al carried out the same or equivalent methods steps and produced the same or equivalent mutant/attenuated Pertussis toxin as now claimed. Inherently the reference

anticipates the now claimed invention in light of extrinsic evidence provided by Rappuoli et al (US PG-Pub 2002/0187154) who teach detoxified Pertussis toxin evidences adjuvant activity (title, abstract claims).

Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

Conclusion

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Various references are being cited that show attenuated toxins.

12. This is a non-final action.

13. The examiner of record has also changed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
September 20, 2010

/Mark Navarro/
Primary Examiner, Art Unit 1645